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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Ulrich Klar et al.	:	Group Art Unit: 1625
Serial No.: 09/485,292	:	Examiner: C. C. Chang
Filed: 3 May 2000	:	

For: NEW EPOTHIOLONE DERIVATIVES, PROCESS FOR THEIR PRODUCTION, AND THEIR PHARMACEUTICAL USE

APPEAL BRIEF

Mail Stop: Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed December 14, 2006, please consider the following. The attached check includes the fee as set forth under § 41.20(b)(2). The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

(i) REAL PARTY IN INTEREST

The real party in interest is Schering A.G.

(ii) RELATED APPEALS AND INTERFERENCES

There are no known related appeals or interferences.

(iii) STATUS OF CLAIMS

Claims 1, 2, 5, 6, 8-12, 31 and 32 are pending in the present application.

Claims 13-30 have been withdrawn from consideration and subsequently cancelled.

Claims 3, 4, 7 and 13-30 have been cancelled.

Claims 1, 2, 5, 6, 8-12, 31 and 32 were rejected.

Claims 1, 2, 5, 6, 8-12, 31 and 32 are on appeal. (A copy of the Claims on Appeal is provided in the attached Appendix.)

(iv) STATUS OF AMENDMENTS

No amendments after the last final rejection were filed.

(v) SUMMARY OF CLAIMED SUBJECT MATTER

Appellants' invention is directed to a compound of formula I as depicted in independent claim 1. See page 3, line 3 to page 4, line 19.

The invention also relates to a compound of formula Ia as depicted in independent claim 2. See page 1, first paragraph which structurally depicts naturally occurring Epothilone A and B and page 3, line 3 to page 4, line 19 for the definitions of Y, Z, R^{1a}, R^{1b}, R^{2a} and R^{2b}.

The invention also relates to a compound of formula Ib as depicted in independent claim 5. See page 1, first paragraph which structurally depicts naturally occurring Epothilone A and B and page 3, line 3 to page 4, line 19 for the definitions of Y, Z, R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^3, R^{4a}, R^{4b}, D-E, R^5, R^6 and R^7.

The invention also relates to a compound of formula I as depicted in dependent claim 6. See page 3, line 3 to page 4, line 19 and original claim 6.

The invention also relates to a compound of formula I as depicted in independent claim 8. See page 10, line 25 to page 19, line 10 and original claim 8.

The invention also relates to a process for the production of an Epothilone compound according to claim 1 as depicted in dependent claim 9. See entire page 5, page 74 to page 77 and original claim 9.

The invention also relates to a pharmaceutical composition comprising a therapeutically effective amount of at least one compound of general formula I, as set forth in dependant claim 10. See page 80 to page 81 and original claim 10.

The invention also relates to the production of a pharmaceutical agent comprising mixing a therapeutically effective amount of a compound of formula I together with a pharmaceutically compatible vehicle, as set forth in claim 11. See page 80-81 and original claim 11.

The invention also relates to a process of preparing a compound of formula A according to independent claim 12. See also page 21, last paragraph to page 22 last paragraph.

The invention also relates to a compound of dependent claim 31. See also, page 3, line 3 to page 4, line 19 for the definitions of R^{2a}, R^{2b}, D-E, and Y.

The invention also relates to a compound of independent claim 32. See also, page 10, line 25 to page 19, line 10 and original claim 8.

(vi) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection are:

A) The rejection of Claims 1-2, 5-6, 9-12 and 31under 35 U.S.C. §112.

B) The double patenting rejection over allowed claims 1-5, 17-18, 20-21 (sic) or 10/631,011 or the claims of US 6,610,736

C) The rejection under 35 U.S.C. § 103 of Claims 1-2, 5-6, 9-12 and 31 over Nicolaou et al.

D) The rejection under 35 U.S.C. § 103 of Claims 8 and 32 over Danishefsky (US 6,242,469).

(vii) ARGUMENT

(A) Rejections under 35 USC §112, first paragraph

Claims 1-2, 5-6, 9-12 and 31stand rejected under 35 U.S.C. §112. The rejection is respectfully traversed.

Appellants' remain confused with regards to the objection to the recitation of "one of R^{10} and R^{11} is H, and the other is 2-Methyl-4-thiazoyl" since this recitation is no longer present in the claims.

Claims 1, 6, 9-12 and 31 do not contain and never did contain the recitation "one of R^{10} and R^{11} is H, and the other is 2-Methyl-4-thiazoyl". Thus, the rejection is based on a recitation that is not present in the claims. Only claims 2 and 5 previously contained the recitation "one of R^{10} and R^{11} is H, and the other is 2-Methyl-4-thiazoyl" and in the amendment of 17 February 20006, at the Examiners suggestion, the limitation was removed and claims 2 and 5 were made independent claims depicting the structural formula of naturally occurring Epothilone A or B along with the original variables presented in claims 2 and 5. The specification provides ample support for the amendment and a "generic description" thereof since the originally presented claims 2 and 5 recited the phrase "the remainder of the molecule is identical to naturally occurring Epothilone A or B" and the first paragraph of the specification provides a structure and reference to naturally occurring

Epothilone A and B. The naturally occurring formula shown on page 1 clearly shows the 2-methyl-4-thiazolyl structure. The subgenus, as currently claimed, with this moiety finds support in original claims 2 and 5.

Thus, the rejection should be withdrawn, particularly since none of the claims contain the objected to recitation "one of R^{10} and R^{11} is H, and the other is 2-Methyl-2-thiazoyl."

B) The Obviousness-type Double Patenting Rejection

The claims (apparently all the claims, since the Office Action does not state which ones) stand rejected for obviousness-type double patenting over "allowed claims 1-5, 17-18, 20-21(sic) or 10/631,011." Appellants previously requested clarification regarding which application this rejection is based on with regards to allowed claims 1-5, 17-18, and 20-21, because the 10/631,011 does not contain such allowed claims and, in fact is now issued as Pat. No. 7,129,254. No clarification was provided. Thus, although the Examiner does not mention the 09/913,163 application in this rejection or in the previous rejection, Appellants will again base their comments on the assumption that the Examiner is possibly referring to allowed claims 1-5, 17-18 and 20-21 of the 09/913,163 application because this was the application that was referred to in the Office Action of 17 October 2005. A terminal disclaimer has already been filed in the 09/913,163 application referring to this application and, thus, according to the PTO rules, a further terminal disclaimer is not required here. The 09/913,163 application has also now issued as Pat. No. 7,001,916.

The claims also stand rejected for obviousness-type double patenting over US Pat. No. 6,610,736. The Examiner has not addressed the distinction pointed out in the response filed February 2006, i.e., that the claims of US 6,610,736 require the R^8 group to be cyano or halogen. The present claims do not include compounds where R^8 is cyano or halogen. In view of this, there is no basis alleged by the Examiner for why the instant claims would be obvious variants of the patent claims. The claims are clearly distinct from those of the '736 patent.

To the extent that the claims may also be subject to an obviousness-type double patenting rejection over the 10/631,011 application (Pat. No. 7,129,254), the '011 application is directed to an effector conjugate that requires a structure of formula III or IV. The Examiner alleges that 10/631,011 teaches esterified pro-drugs and that pro-drug conjugates are obvious formulation of compounds for delivery purposes. Regardless of any prodrug effect, the claims do not encompass the same subject matter. Furthermore, nothing in the

claims of the '011 application teaches or suggests the breaking up of the claimed conjugates to obtain the partial structures as separate compounds. Thus, the instant claims are directed to patentably distinct subject matter and are not obvious variants of the claims of the '011 application. The Examiner merely makes the conclusory statement that a pro-drug is obvious. No legal or scientific support or other reasoning is provided. Thus, no motivation to support obviousness is provided.

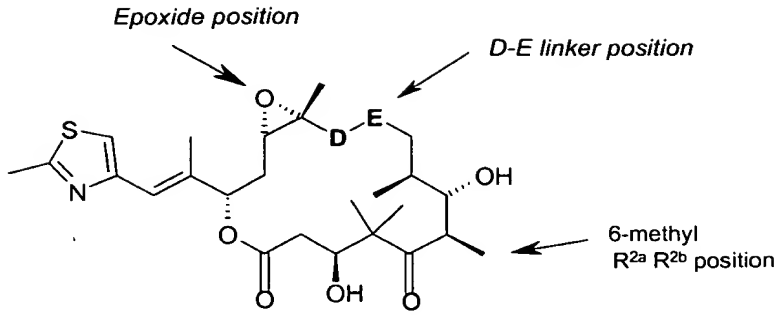
Withdrawal of the obviousness-type double patenting rejection is respectfully requested.

C) The Rejections of Claims 1-2, 5-6, 9-12 and 31 under 35 U.S.C §103 as being unpatentable over Nicolaou et al. (CA 132:293587)

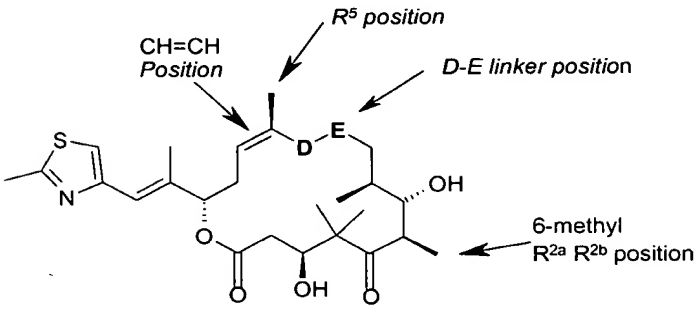
The obviousness rejection of Claims 1-2, 5-6, 9-12 and 31 under 35 U.S.C §103 as being unpatentable over Nicolaou et al. was set forth in the office action dated March 4, 2004. The rejection is based on the premise of homology at the R^{2a} and R^{2b} positions. The prior art compound of Nicolaou and the claimed invention are homologues with respect to an alkyl group at the R^{2a} and R^{2b} positions. Like the compound of Nicolaou, Epothilone B and Epothilone D are also homologues with respect to an alkyl group at the R^{2a} and R^{2b} positions. In response to the rejection, Appellants' submitted a 37 CFR 1.132 declaration by Dr. Klar (on 7 September 2004), which demonstrated the advantage of replacing the 6-methyl group in natural Epothilone B and Epothilone D with a higher alkyl substituent. A copy of the declaration is attached in the Appendix.

At page 5 and again at page 7 of the 14 September 2006 Office Action, the Examiner exemplifies Epothilone B and Epothilone D and alleges that "all 21 compounds presented by the (Klar) declaration either have the DE is epoxy or the DE is CH=CH." As Appellants previously pointed out in the response of 4 August 2006, this is incorrect. The D-E linker is CH_2-CH_2 in all 21 compounds presented by the Klar declaration. Clarification was respectfully requested but the rejection was reiterated.

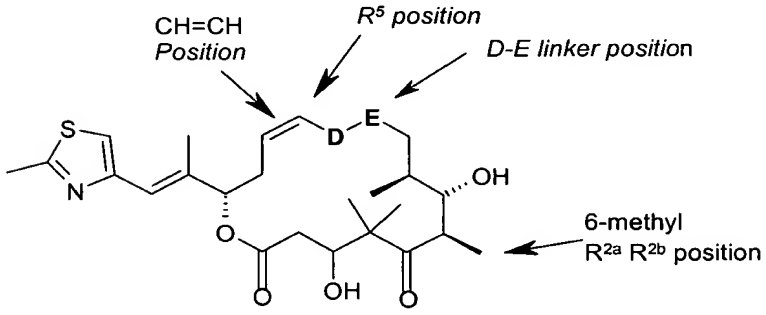
Appellants note that R^6 and R^7 of Appellants formula I correspond to the epoxy portion of Epothilone B. In the case of Epothilone D, R^6 and R^7 of Appellants' formula I corresponds to the CH=CH structure. See the following formulae showing these structures.



Epothilone B



Epothilone D



Nicolaou

All of the tested compounds presented in the declaration of Dr. Klar contain the $-CH_2-CH_2-$ linker (D-E linker) that is present in Nicolaou's compound. Thus, the claimed compounds compared and the Nicolaou compounds have the same structure at the D-E linker position.

The following comments are based upon the assumption that the Examiner may be referring to the R^5 methyl that is present on the test compounds but not Nicolaou's compound. The prior art compound and the claimed invention are homologues with respect to the alkyl

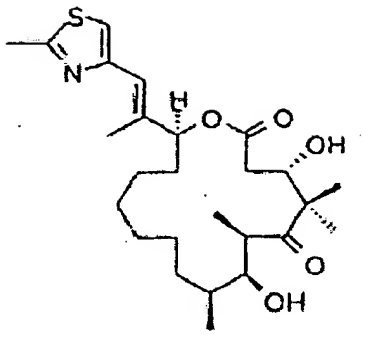
group at the R^{2a} and R^{2b} positions. The proviso portion of the instant claims recites "...whereby, if -D-E- stands for $-CH_2-CH_2-$ and Y stands for an oxygen atom, at least one of R^{2a} and R^{2b} is not hydrogen or methyl." Thus, Nicolaou's compound, which contains a methyl at one of the R^{2a} and R^{2b} positions, is already excluded based on this proviso. Appellant's burden is to overcome the obviousness rejection based on the premise of homology at the R^{2a} and R^{2b} positions. The declaration includes test of compounds, which meet the proviso against compounds in which -D-E- stands for $-CH_2-CH_2-$ and Y stands for an oxygen atom and at least one of R^{2a} and R^{2b} is methyl, as is the case with Nicolaou's compound. As stated in the Declaration, the data shows that the compounds with a higher alkyl group generally exhibit significantly greater activity against known human tumor cell lines, have advantageous antiproliferative properties (lower IC_{50} values) and have improved sensitivity to multi-drug resistant (MDR) cell lines.

Thus, regardless of the addition of the R^5 methyl group, the declaration has demonstrated that compounds that differ by a methylene linkage at the R^{2a} and R^{2b} positions show unexpected properties. Appellants' burden of proof has been met. No further test data should be required. Such would be essentially redundant, would require the inventor to synthesize additional compounds and would seem to serve for nothing except to perhaps unduly burden the inventor. Thus, the presumption of similar properties based on homology at the R^{2a} and R^{2b} positions, which forms the basis for the rejection, is disproved and the rejection should be withdrawn.

D) The rejection of Claims 8 and 32 under 35 U.S.C §103 as being unpatentable over Danishefsky (US 6,242,469).

Claims 8 and 32 stand rejected under 35 U.S.C §103 as being unpatentable over Danishefsky (US 6,242,469). The Examiner is relying upon the provisional application filing date of 3 December 1996 as the prior art date for the reference. However, as previously pointed out in the response filed 4 August 2006, Figure 42B (or a structure corresponding to compound 34 of Figure 42B) is not present in this earlier filed provisional application. Thus, the figure 42B disclosure does not have support in the earlier provisional application and its later disclosure, in the non-provisional filing, is not prior art against the instant claims. Since compound 34 of Figure 42B was primarily relied on as the basis for rejection, the rejection should be withdrawn.

In any event, the rejection points to compound 34 of Figure 42B, depicted below.



34
(0.143)
[0.276]

Thus, like Nicolaou et al., Danishefsky's compound 34 of Figure 42B has a methyl at one of the R^{2a} and R^{2b} positions and is excluded based upon the proviso which recites "...whereby, if -D-E- stands for $-CH_2-CH_2-$ and Y stands for an oxygen atom, at least one of R^{2a} and R^{2b} is not hydrogen or methyl." Furthermore, the comparative data, presented in the declaration of Dr. Klar, applies equally. The comparative data clearly demonstrates the advantage of replacing the 6-methyl group with a higher alkyl substituent.

Reversal of the rejection is respectfully and courteously requested.

Respectfully submitted,

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Attorney Docket No.: SCH-1742
Date: **23 February 2007**
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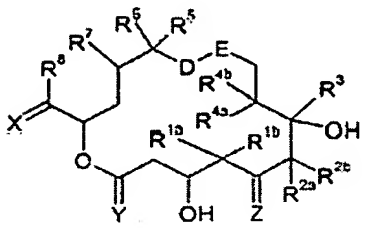
(viii) CLAIMS APPENDIX

Listing of Claims on Appeal:

1. An epothilone compound of formula I,



in which

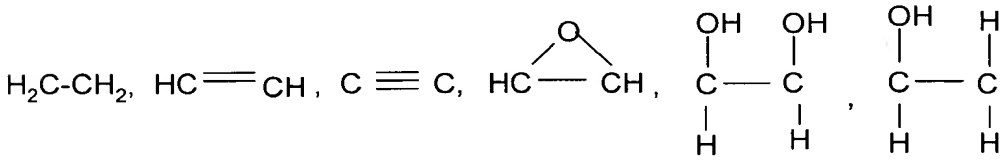
R^{1a}, R^{1b} are the same or different and mean hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, or together a -$(CH_2)_m$- group with m = 2, 3, 4 or 5,

R^{2a}, R^{2b} are the same or different and mean hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl or together a -$(CH_2)_n$- group with n = 2, 3, 4 or 5, whereby, if -D-E- stands for -CH_2-CH_2- and Y stands for an oxygen atom, at least one of R^{2a} and R^{2b} is not hydrogen or methyl,

R^3 means hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl,

R^{4a}, R^{4b} are the same or different and mean hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl or together a -$(CH_2)_p$- group with p = 2, 3, 4 or 5,

D-E means a group



R^5 means hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl,

R^6, R^7 each mean a hydrogen atom, together an additional bond or an oxygen atom,

R^8 means hydrogen, C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl, which can all be substituted,

X means an oxygen atom, two alkoxy groups OR^{23}, a C_2-C_{10} alkylene-"α,ω--dioxy group, which can be straight-chain or branched, H/OR^9 or a grouping $CR^{10}R^{11}$,

whereby

R^{23} stands for a C_1-C_{20} alkyl radical,

R^9stands for hydrogen or a protective group PG^x,

R^{10}, R^{11} are the same or different and stand for:

hydrogen;

a C_1-C_{20} alkyl radical;

a substituted or unsubstituted phenyl, naphthyl, furyl, thienyl, pyridyl, pyrazolyl, pyrimidinyl, oxazolyl, pyridazinyl, pyrazinyl, quinolyl or thiazolyl radical; or

a C_7-C_{20} aralkyl radical; or

R^{10} and R^{11} together with the methylene carbon atom together stand for a 5- to 7-membered carbocyclic ring,

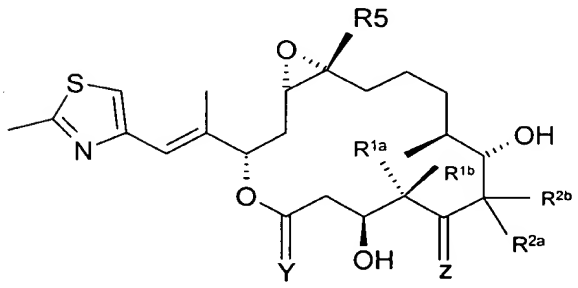
Y means an oxygen atom or two hydrogen atoms,

Z means an oxygen atom or H/OR^{12},

whereby

R^{12} means hydrogen or a protective group PG^z.

2. An epothilone compound of formula Ia



(Ia)

in which

R^{1a}, R^{1b} are the same or different and mean hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, or together a $-(CH_2)_m-$ group with m = 2, 3, 4 or 5,

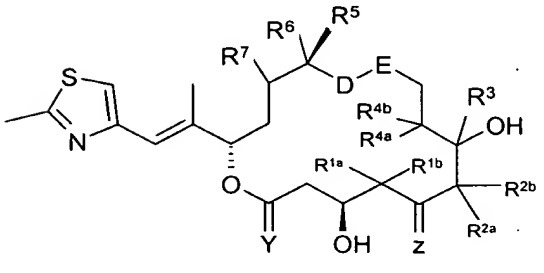
R^{2a}, R^{2b} are the same or different and mean hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl or together a $-(CH_2)_n-$ group with n = 2, 3, 4 or 5, whereby, if Y stands for an oxygen atom, at least one of R^{2a} and R^{2b} is not hydrogen or methyl,

R^5 is H or CH_3

Y means an oxygen atom or two hydrogen atoms, and

Z means an oxygen atom or H/OR^{12}.

5. An epothilone compound of formula Ib



(Ib)

in which

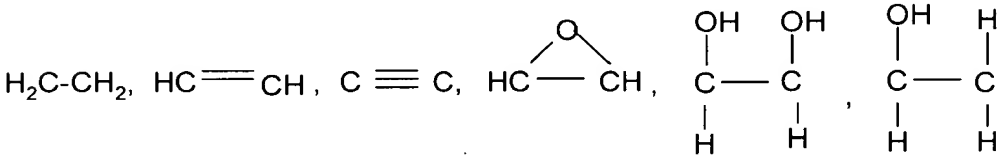
R^{1a}, R^{1b} are the same or different and mean hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl, or together a -$(CH_2)_m$- group with m = 2, 3, 4 or 5,

R^{2a}, R^{2b} are the same or different and mean hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl or together a -$(CH_2)_n$- group with n = 2, 3, 4 or 5, whereby, if -D-E- stands for -CH_2-CH_2- and Y stands for an oxygen atom, at least one of R^{2a} and R^{2b} is not hydrogen or methyl,

R^3 means hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl,

R^{4a}, R^{4b} are the same or different and mean hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl or together a -$(CH_2)_p$- group with p = 2, 3, 4 or 5,

D-E means a group



R^5 means hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl,

R^6, R^7 each mean a hydrogen atom, together an additional bond or an oxygen atom,

Y means an oxygen atom or two hydrogen atoms, and

Z means an oxygen atom or H/OR^{12}.

6. An epothilone compound of formula I according to claim 1, in which Y, Z, R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^6, R^7, R^8 and X all have the meanings that are indicated in formula I, and

R^3 is H,

one R^{4a} and R^{4b} is H and the other is methyl,

R^5 is H or methyl

and

D-E is H_2C-CH_2.

8. A compound of formula I, namely

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione (B),

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione ,

(1R,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione ,

(1R,3S(E),7S,10R,11S,12S,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7S,8R,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione,

(4S,7S,8R,9S,13E,16S(E))-4,8-dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10S,11R,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

(1R,3S(E),7S,10S,11R,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10S,11R,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

(1R,3S(E),7S,10S,11R,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-7-phenyl-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-phenyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

(1R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-phenyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13(E or Z),16S(E))-7-Benzyl-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,16R)-10-Benzyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

(1R or S),3S(E),7S,10R,11S,12S,16S)-10-Benzyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,11E/Z,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-11,13-diene-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,14E/Z,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione,

(1R or S),3S(E),7S,10R,11S,12S,14E/Z,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione,

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-11-ine-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ine-5,9-dione,

(1R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ine-5,9-dione,

(4S,7R,8S,9S,11E/Z,13(E or Z),16S(E))-4,8-Dihydroxy-13-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9-tetramethyl-cyclohexadec-11,13-

diene-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,14E/Z,16R)-7,11-Dihydroxy-16-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione,

(1R or S),3S(E),7S,10R,11S,12S,14E/Z,16S)-7,11-Dihydroxy-16-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione,

(4S,7R,8S,9S,11E/Z,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-13-propyl-5,5,7,9-tetramethyl-cyclohexadec-11,13-diene-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,14E/Z,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-16-propyl-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione,

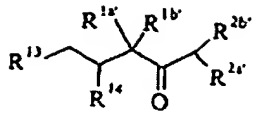
(1R or S),3S(E),7S,10R,11S,12S,14E/Z,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-16-propyl-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione,

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-9-one, or

(1R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-9-one.

9. A process for the production of an epothilone compound according to claim 1

reacting a fragment of general formula A



A,

in which

$R^{1a'}$, $R^{1b'}$, $R^{2a'}$ and $R^{2b'}$ have the meanings already mentioned for R^{1a}, R^{1b}, R^{2a} and R^{2b},

R^1 means CH_2OR^{13a}, CH_2-Hal, CHO, CO_2R^{13b}, COHal,

R^1 means hydrogen, OR^{14a}, Hal, OSO_2R^{14b},

R^{13a}, R^{14a} mean hydrogen, SO_2-alkyl, SO_2-aryl, SO_2-aralkyl or together a $-(CH_2)_o$ group or together a $CR^{15a}R^{15b}$ group,

R^{13b}, R^{14b} mean hydrogen, C_1-C_{20} alkyl, aryl, C_1-C_{20} aralkyl,

R^{15a}, R^{15b} are the same or different and mean hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl or together a $-(CH_2)_q$-group,

Hal means halogen,

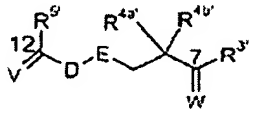
o means 2 to 4,

q means 3 to 6,

including all stereoisomers as well as their mixtures, and

free hydroxyl groups in R^{13} and R^{14} can be etherified or esterified, free carbonyl groups can be ketalized in A and R^{13}, converted into an enol ether or reduced, and free acid groups in A can be converted into their salts with bases,

with a fragment of general formula B



B

in which

$R^{3'}$, $R^{4a'}$, $R^{4b'}$ and $R^{5'}$ have the meanings already mentioned for R^3, R^{4a}, R^{4b} and R^5,

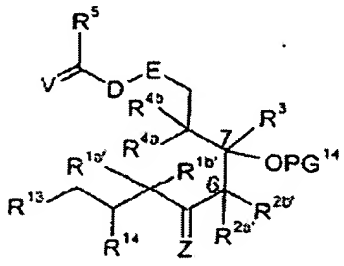
V means an oxygen atom, two alkoxy groups OR^{17}, a C_2-C_{10} alkylene-α,ω--dioxy group, which can be straight-chain or branched or H/OR^{16},

W means an oxygen atom, two alkoxy groups OR^{19}, a C_2-C_{10} alkylene- α,ω--dioxy group, which can be straight-chain or branched or H/OR^{18},

R^{16}, R^{18}, independently of one another, mean hydrogen or a protective group PG^1

R^{17}, R^{19}, independently of one another, mean C_1-C_{20} alkyl,

to a form a compound of partial fragment of formula AB

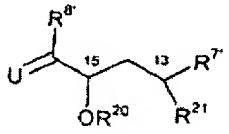


AB,

in which $R^{1a'}$, $R^{1b'}$, $R^{2a'}$, $R^{2b'}$, R^3, R^{4a}, R^{4b}, R^5, R^{13}, R^{14}, D, E, V and Z have the meanings already mentioned, and PG^{14} represents a hydrogen atom or a protective group PG,

and,

reacting this compound of partial fragment AB is reacted with a fragment of general formula C



C

in which

$R^{8'}$ has the meaning already mentioned in general formula I for R^8, and

$R^{7'}$ means a hydrogen atom,

R^{20} means a hydrogen atom or a protective group PG^2,

R^{21} means a hydroxy group, halogen, a protected hydroxy group OPG^3, a phosphonium halide radical $PPh_3^+Hal^-$ (Ph = phenyl; Hal = F, Cl, Br, I), a phosphonate radical $P(O)(OQ)_2$ (Q = C_1-C_{10} alkyl or phenyl) or a phosphine oxide radical $P(O)Ph_2$ (Ph = phenyl),

U means an oxygen atom, two alkoxy groups OR^{23}, a C_2-C_{10} alkylene-α,ω--dioxy

group, which can be straight-chain or branched, H/OR^9 or a grouping $CR^{10}R^{11}$,

whereby

R^{23} stands for a C_1-C_{20} alkyl radical,

R^9 stands for hydrogen or a protective group PG^3,

R^{10}, R^{11} are the same or different and stand for:

hydrogen;

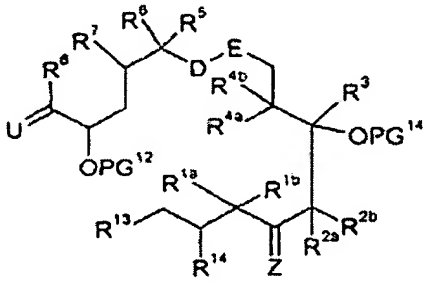
a C_1-C_{20} alkyl radical;

a substituted or unsubstituted phenyl, naphthyl, furyl, thienyl, pyridyl, pyrazolyl, pyrimidinyl, oxazolyl, pyridazinyl, pyrazinyl, quinolyl or thiazolyl radical; or

a C_7-C_{20} aralkyl radical or

R^{10} and R^{11} together with the methylene carbon atoms together stand for a 5- to 7-membered carbocyclic ring,

to obtain a compound of a partial fragment of formula ABC



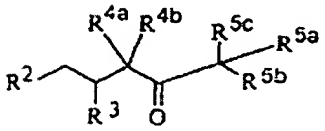
ABC,

in which $R^{1a'}$, $R^{1b'}$, $R^{2a'}$, $R^{2b'}$, R^3, R^{4a}, R^{4b}, R^5, R^6, R^7, R^8, R^{13}, R^{14}, D, E, U and Z have the meanings already mentioned, and this compound of partial fragment of formula ABC is cyclized to an epothilone derivative of general formula I.

10. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of general formula I according to claim 1, as well as a pharmaceutically compatible vehicle.

11. A method for the production of a pharmaceutical agent comprising mixing a therapeutically effective amount of a compound of formula I according to claim 1, together with a pharmaceutically compatible vehicle.

12. A process for the production of a compound of formula A



A,

in which

R^2 means CH_2OR^{2a}, CHO, CO_2R^{2b}, COX,

R^{2a}, R^{2b} mean hydrogen, C_1-C_{20} alkyl, aryl, C_7-C_{20} aralkyl,

R^3 means hydrogen, OR^{3a}, X, OSO_2R^{3b},

R^{3a} means hydrogen or together with R^{2a} a $-(CH_2)_n-$ group or a $CR^{6a}R^{6B}$ group,

R^{3b} means C_1-C_4 alkyl, aryl,

X means halogen,

n means 2 to 4,

R^{6a}, R^{6b} are the same or different and mean C_1-C_8 alkyl, C_6-C_{10} aryl or together a $-(CH_2)_o-$ group,

o means 3 to 6,

R^{6a} additionally can assume the meaning of hydrogen,

R^{4a}, R^{4b} are the same or different and mean hydrogen, C_1-C_{10} alkyl, C_7-C_{20} aralkyl or together a $-(CH_2)_m-$ group,

m means 2 to 5

R^{5a}, R^{5b} are the same or different and mean hydrogen, C_1-C_{10} alkyl, C_7-C_{20} aralkyl or together a $-(CH_2)_p-$ group,

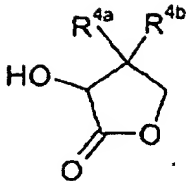
p means 2 to 5

R^{5c} means hydrogen,

including all steroisomers and mixtures thereof, and

free hydroxyl groups can be etherified or esterified in R^2 and R^3, free carbonyl groups can be ketalized in A and R^2, converted into an enol ether or reduced, and free acid groups in A can be converted into their salts with bases, wherein

a) a pantolactone of formula IIa or

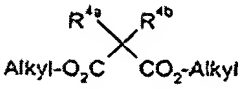


IIa

in which

R^{4a} and R^{4b} in each case are methyl groups or

b) a malonic acid dialkyl ester of formula XXVIII



XXVIII

in which

R^{4a}, R^{4b}, which have the meaning that is indicated in formula A, and alkyl, independently of one another, mean a C_1-C_{20} alkyl, C_3-C_{10} cycloalkyl or C_4-C_{20} alkylcycloalkyl radical, is used as a starting product.

31. A compound of claim 1, in which

R^{2a}, R^{2b} are the same or different and mean hydrogen, C_1-C_{10} alkyl, aryl, C_7-C_{20} aralkyl or together a $-(CH_2)_n-$ group with n = 2, 3, 4 or 5,

whereby, if -D-E- stands for

$-CH_2-CH_2-$ or Y stands for an oxygen atom, then R^{2a} and R^{2b} cannot be hydrogen or C_1-C_{10} alkyl.

32. A compound which is:

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-((3-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-((3-

pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-((3-pyridyl)ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-((3-pyridyl)ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-((4-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione,

(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-((4-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione,

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-((4-pyridyl)ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-((4-pyridyl)ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,13-tetramethyl-9-trifluoromethyl-cyclohexadec-13-ene-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,16-tetramethyl-12-trifluoromethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

(1R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,16-tetramethyl-12-trifluoromethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

(1R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-

methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ine-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9-tetramethyl-13-trifluoromethyl-cyclohexadec-13-ene-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-16-trifluoromethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(1R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12-tetramethyl-16-trifluoromethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-13-pentafluoroethyl-5,5,7,9-tetramethyl-cyclohexadec-13-ene-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-16-pentafluoroethyl-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(1R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-16-pentafluoroethyl-8,8,10,12-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5-(1,3-trimethylene)-7,9,13-trimethyl-cyclohexadec-13-ene-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylene)-10,12,16-trimethyl-4,17-

dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(1R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8-(1,3-trimethylene)-10,12,16-trimethyl-4,17-dioxabicyclo[14.1.0]heptadeca-5,9-dione,

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

(1R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(4-pyridyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-2,6-dione,

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(4-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

(1R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(4-pyridyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione, or

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-6-one.

(ix) EVIDENCE APPENDIX

Declaration of Dr. Klar under 37 CFR§1.132 submitted 7 September 2004 and acknowledged by the Examiner at page two of the Office Action mailed 2 August 2005.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

Ulrich Klar et al. : Group Art Unit: 1614

Serial No.: 09/485,292 : Examiner: Binta Robinson

Filed: 3 May 2000 :

For: NEW EPOTHIOLONE DERIVATIVES, PROCESS FOR THEIR PRODUCTION, AND THEIR PHARMACEUTICAL USE

132 DECLARATION

Sir:

I, Ulrich Klar, being duly warned, declare that:

I am an inventor identified in the above-captioned application and am familiar with the invention described therein and with the grounds alleged for rejection made against the claims of the application in the Office Action mailed 4 March 2004.

The following experiments were conducted by me or under my supervision to show the advantage of replacement of the 6-methyl group in the natural compounds Epothilone B and Epothilone D by an ethyl or other higher alkyl substituent. The data unexpectedly demonstrate that the compounds with ethyl or other higher alkyl substituents have significantly better activity (i.e., lower IC_{50}) in more tumor cell lines and better sensitivity to the multi-drug-resistant cell line NCI/ADR compared to MCF-7 than the corresponding compounds with methyl substitution.

The tumor cell lines used for the in vitro assays are of human origin. It is well accepted in the scientific community that the inhibition of tumor cell proliferation especially of different tumor cell lines of one tumor type (e.g. breast, lung, ovary etc.) are an indication that the compound may be useful in the treatment of this type of cancer also in vivo. Because not all of these tumor cell lines grow in vivo and due to our animal protecting laws, in vivo experiments can be performed only for a very limited number of compounds which are selected upon their in vitro profile.

In the following overview the unexpected beneficial effects observed by replacing the 6(10)-methyl group present in all naturally occurring epothilones by an alkyl-group is demonstrated.

The following data would demonstrate to the normally skilled researcher in this technology that the ethyl and higher alkyl compounds have significantly advantageous properties compared to the corresponding methyl compounds.

1. Effect on activity

Compared are the IC_{50} values obtained for different human tumor cell lines of a 6(10)-alkyl compound (right columns) with its corresponding 6(10)-methyl reference compound (middle columns). To demonstrate the broad usefulness of these unexpected findings, different types of epothilones are listed in Tables 1 to 4 as examples. Beside the naturally occurring epothilone B (Table 1) and epothilone D (Table 2) also synthetic analogs bearing several structural modifications at different regions of the molecule were investigated (Tables 3 to 4). The data unexpectedly demonstrate that the replacement of the 6(10)-methyl group by an alkyl group in different types of epothilones enhances the antiproliferative activity (lower IC_{50} values).

Table 1: Replacement of the 6-methyl group in the natural compound Epothilone B by an ethyl group enhances the activity.

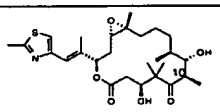
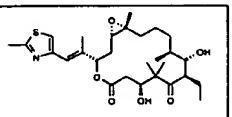
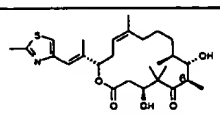
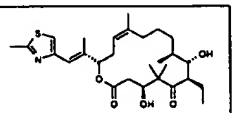
Table 1	 Epothilone B (Ref. 1)	
MCF-7	0.59 nM	< 0.24 nM
NCI/ADR	3.5 nM	0.43 nM
MaTu	0.46 nM	< 0.24 nM
MaTu/ADR	1.2 nM	< 0.19 nM
A 431	0.43 nM	< 0.1 nM
H460	0.35 nM	< 0.1 nM

Table 2: Replacement of the 6-methyl group in the natural compound Epothilone D by an ethyl group enhances the activity.

Table 2	 Epothilone D (Ref. 1)	

MCF-7	19 nM	4.4 nM
MaTu	13 nM	6.3 nM
MaTu/ADR	37 nM	5.8 nM

Table 3: Replacement of the 6-methyl group in the synthetic reference compound 3 by a hydroxy-butyl group enhances the activity.

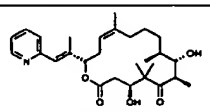
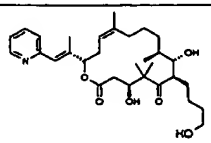
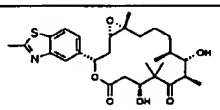
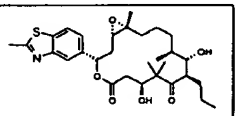
Table 3	 (Ref. 3)	
MCF-7	5.6 nM	3.5 nM
MaTu	5.4 nM	2.3 nM

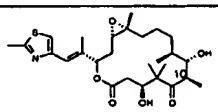
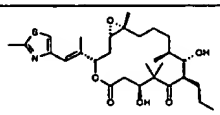
Table 4: Replacement of the 6-methyl group in the synthetic reference compound 4 by a propyl group enhances the activity.

Table 4	 (Ref. 4)	
MaTu	0.44 nM	0.2 nM
MaTu/ADR	0.81 nM	0.58 nM

2. Effect on overcoming multi-drug-resistance

Beside the overall activity it is desired not to lose activity against such human tumor cells which had already acquired marked resistancies. In Tables 5 to 10 the effect of replacing the 6(10)-methyl group by an alkyl group in different types of epothilones on the relative sensitivity to a human tumor cell lines overexpressing the multidrug resistance (MDR) phenotype is discussed. The relative sensitivity is defined as quotient of the IC_{50}-values of a parent human tumor cell line (MCF7 or MaTu) and its corresponding MDR cell line (NCI/ADR or MaTu/ADR). This quotient is set to 100% for the reference compound bearing the 6(10)-methyl group. A value above 100% for the 6(10)-alkyl compound therefore indicates an improved sensitivity of the compound against the MDR cell line compared to its corresponding 6(10)-methyl reference compound.

Table 5: Replacement of the 6-methyl group in the natural compound Epothilone B by a propyl group enhances the relative sensitivity by 353%.

Table 5	 Epothilone B (Ref. 1)	
MCF-7	0.59 nM	3.4 nM

NCI/ADR	3.5 nM	4.3 nM
Ratio MCF7:NCI/ADR	0.17 (100%)	0.77 (453%)

Table 6: Replacement of the 6-methyl group in the natural compound Epothilone D by a propyl group enhances the relative sensitivity by 32% and 114%, respectively.

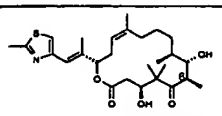
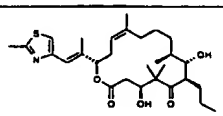
Table 6	 Epothilone D (Ref. 2)	
MCF-7	19 nM	38 nM
NCI/ADR	50 nM	76 nM
Ratio MCF7:NCI/ADR	0.38 (100%)	0.5 (132%)
MaTu	13 nM	36 nM
MaTu/ADR	37 nM	48 nM
Ratio MaTu:MaTu/ADR	0.35 (100%)	0.75 (214%)

Table 7: Replacement of the 6-methyl group in the synthetic reference compound 7 by an ethyl group enhances the relative sensitivity by 208% and 186%, respectively.

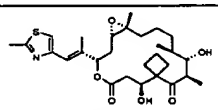
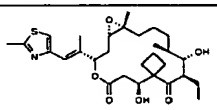
Table 7	 (Ref. 7)	
MCF-7	0.47 nM	1.6 nM
NCI/ADR	3.6 nM	4 nM
Ratio MCF7:NCI/ADR	0.13 (100%)	0.4 (308%)
MaTu	0.46 nM	1.2 nM
MaTu/ADR	1.3 nM	1.2 nM
Ratio MaTu:MaTu/ADR	0.35 (100%)	1.0 (286%)

Table 8: Replacement of the 6-methyl group in the synthetic reference compound 3 by an ethyl or propyl group enhances the relative sensitivity by 147% or 68%, respectively.

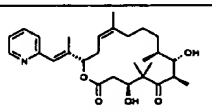
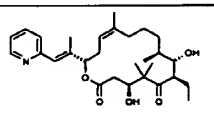
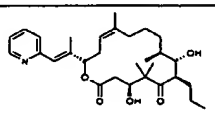
Table 8	 (Ref. 3)		
MCF-7	5.6 nM	23.5 nM	26 nM
NCI/ADR	29 nM	50 nM	81 nM
Ratio MCF7:NCI/ADR	0.19 (100%)	0.47 (247%)	0.32 (168%)

Table 9: Replacement of the 6-methyl group in the synthetic reference compound 8 by an ethyl group enhances the relative sensitivity by 203% and 153%, respectively.

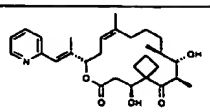
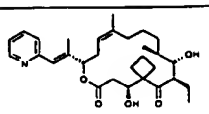
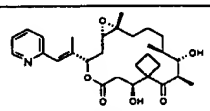
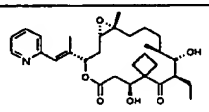
Table 9	 (Ref. 8)	
MCF-7	22 nM	33 nM
NCI/ADR	56 nM	28 nM
Ratio MCF7:NCI/ADR	0.39 (100%)	1.18 (303%)
MaTu	8.8 nM	31 nM
MaTu/ADR	29 nM	41 nM
Ratio MaTu:MaTu/ADR	0.30 (100%)	0.76 (253%)

Table 10: Replacement of the 6-methyl group in the synthetic reference compound 9 by an ethyl group enhances the relative sensitivity by 1592%.

Table 10	 (Ref. 9)	
MaTu	0.49 nM	1.1 nM
MaTu/ADR	4.1 nM	0.54 nM
Ratio MaTu:MaTu/ADR	0.12 (100%)	2.03 (1692%)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Ulrich Klar 16.08.2004

Ulrich Klar Date

(x) RELATED PROCEEDINGS APPENDIX

None